BIOLOGICAL ACTIVITY OF CERTAIN DERIVATIVES OF THIAZOLE

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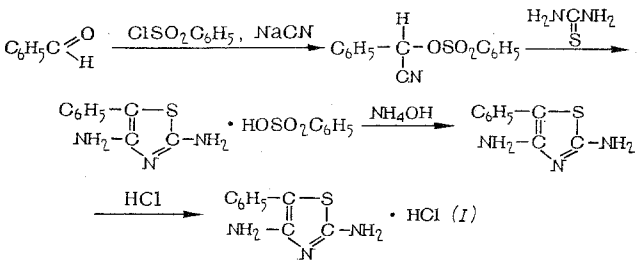
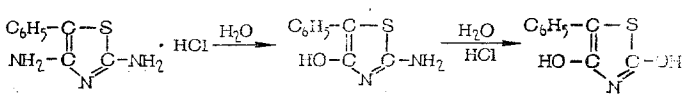
Stimulators of respiration and substances exhibiting an antagonistic action with respect to morphine, nicotine, and barbiturates have been found among thiazole derivatives [1, 2, 3, 4]. One of the most active preparations of this group is 2,4-diamino-5-phenylthiazole hydrochloride [1], known under the name of daptazole. According to the literature data, this preparation is produced in four steps with a total yield of 38% [3].



We have developed a simpler method of synthesis of this compound. The isolation and purification of α-cyanobenzylbenzenesulfonate are eliminated at the stage of its production. At the last step the base is extracted with ethyl acetate and then the hydrochloride is precipitated with dry hydrogen chloride (yield 45-50%).

To study the relationship of the chemical structure and biological properties in this series, we were interested in producing certain derivatives of I with various substituents in the phenyl ring or in the 2,4-positions of the thiazole ring. For this purpose, 2,4-diamino-5-(p-fluorophenyl)thiazole hydrochloride (II) and 2,4-diamino-5-(o-nitrophenyl)thiazole hydrochloride (III), which are crystalline substances readily soluble in water, were produced according to the scheme cited above (see Table 1).

When the hydrochloride I is boiled in water for 6 h, one amino group in the thiazole ring is readily hydrolyzed, and 2-amino-4-hydroxy-5-phenylthiazole is formed. In the presence of concentrated hydrochloric acid, hydrolysis proceeds further, forming 2,4-dihydroxy-5-phenylthiazole.



To obtain water-soluble compounds, we prepared alcoholates of mono- and dihydroxy derivatives of thiazole (IV) and (V), which are crystalline substances, readily soluble in water (see Table 1).

The synthesized substances were subjected to pharmacological evaluation. In acute experiments on mice we studied the toxicity of the substances after intraperitoneal injection (the values of LD_{50}, calculated

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TABLE 1. Physicochemical and Pharmacological Properties of Substances

Compound	Melting point (in degrees C)	HCl found (in %)	Empirical formula	HCl calculated (in %)	Influence on respiration[3]		Influence on arterial pressure[4]	LD_{50} (in mg/kg)
					frequency	amplitude		
I	273 dec.	15,53	$C_9H_9N_3S \cdot HCl$	15,60	+280,0	+51,0	—59,5	159,5±10,0 330±30,5[5]
II	254	—	$C_9H_8FN_3S \cdot HCl$[1]	—	+350,0	+17,8	—30,1	190±10,2
III	154	12,96	$C_9H_8N_4O_2S \cdot HCl$	12,86	+72,7	—	—38,8	158±25,0
IV	194	13,36	$C_9H_7N_2NaOS$[2]	13,02	0	+4,0	—7	>800,0
V	256	6,10	$C_9H_5—NNa_2O_2S$	5,90	—	+0,7	—12,5	420±43,4
VI	255	—	—	—	—	—	—	510±40,5[5]
VII	153	—	—	—	—	—	—	290,0±30,8[5]

[1]Found, %: N 17.01; S 12.90. Calculated %: N 17.03; S 13.06.
[2]Found, %: S 15.21. Calculated, %: S 14.88.
[3]"+" or "—" denotes the average increase or decrease in the frequency and amplitude of the respiratory movements, respectively, in % of the initial value.
[4]"+" or "—" denotes the average increase or decrease in the arterial pressure, respectively, in % of the initial value.
[5]When introduced into the stomach.
Note. Compounds I, VI, and VII have been described in the literature; their melting points correspond to the literature data [5, 6].

by the method of Litchfield and Wilcoxon, are presented in Table 1). Moreover, in acute experiments on rats immobilized with morphine (40 mg/kg intraperitoneally), we investigated the influence of the compounds on respiration and arterial pressure. The data obtained after intravenous injection of the preparations in a dose of 40 mg/kg are presented in Table 1.

A comparison of the results obtained showed that the introduction of substituents into the phenyl ring of I does not significantly change the toxicity, while the replacement of one or two amino groups in the thiazole ring lowers the toxicity of the substances. In view of the poor solubility of the benzenesulfonate of 2,4-diamino-5-phenylthiazole (VI) and the base of daptazole (VII), their toxicity was compared with I introduced into the stomach. As was shown by the experiments, in the case of this mode of introduction VII practically does not differ in toxicity from I, while preparation VI proved considerably less toxic (see Table 1). We should emphasize that the symptoms of poisoning with preparations II-IV differ little from those of I. And yet, the picture of poisoning with preparation V proved different. Thus, 10-15 min after the administration of toxic and subtoxic doses of preparation V to mice, a stupor arises in most of the animals, accompanied by a loss of muscle tone and in certain cases by the appearance of brief clonic convulsions. After this animals assume a side position, and they pass into a state of unique "narcotic sleep;" the corneal reflexes are maintained in this case, but the response to mechanical pain stimulation of the tail is significantly lowered. This state of "sleep" lasts 6-8 h, then a gradual restoration of the turning over reflex sets in, and a state of increased pain sensitivity develops. The state of stiffness comes considerably more rapidly in the mice that die than in the control animals.

The picture of poisoning after the administration of the remaining preparations, including I, is characterized by clonic-tonic convulsions and an increase in the respiration frequency, followed by inhibition of respiration; death occurs within the first 30 min after administration. Daptazole and preparations II, III, IV, VI, and VII do not induce "narcotic sleep."

The experiments showed that the replacement of amino groups in the thiazole ring in the 2- and 4-positions by hydroxyl groups leads to a disappearance of the antimorphine effect on respiration characteristic of I and to the appearance of a number of the peculiarities indicated above in the picture of the toxic action. The introduction of substituents into the phenyl ring does not change the hypotensive nature of the action of the substances.

The most pronounced stimulatory effect on the morphine-inhibited respiration is exhibited by preparations I and II. The action of I is more prolonged.

EXPERIMENTAL

2,4-Diamino-5-phenylthiazole Hydrochloride I. To a mixture of 3.5 g benzaldehyde and 8.8 g benzenesulfonyl chloride, a solution of 2.45 g sodium cyanide in 10 ml of water is added with mixing at 0°C and the mixture is mixed for 2 h at 0°C. The precipitate obtained is filtered off and washed with water to a neutral pH. The α-cyanobenzylbenzenesulfonate is dissolved in 20 ml of acetone, and 3.8 g thiourea is added. The mixture is heated at a temperature of 60°C with a reflux condensor for 30 min until complete dissolution, then the solution is diluted with five times the amount of water and neutralized with an aqueous solution of ammonia to pH 9.0-10.0. The base obtained is extracted with ethyl acetate. Hydrogen chloride is passed through a solution of the base in ethyl acetate, and the hydrochloride precipitates in the form of white crystals, 45% yield.

Preparations II and III are produced analogously (with a yield of 10%).

Sodium Salt of 2-Amino-4-hydroxy-5-phenylthiazole (IV). A 1.5-g portion 2-amino-4-hydroxy-5-phenylthiazole is dissolved in 40 ml of alcohol, and 0.412 g sodium methylate in 10 ml of methanol is added. The solution is boiled for 30 min, and the alcoholate precipitated with ether. Yield 0.75 g (47%).

Disodium Salt of 2,4-Dihydroxy-5-phenylthiazole (V). A 1.5-g portion of 2,4-dihydroxy-5-phenylthiazole is dissolved in 10 ml of methanol. The mixture is boiled for 2 h, and 1 g (55%) of a white crystalline substance precipitates from solution.

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